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Impact of Coronary Lesion Complexity on Drug-Eluting Stent Outcomes in Patients With and Without Diabetes Mellitus

Analysis From 18 Pooled Randomized Trials

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Objectives The aim of this study was to investigate whether baseline lesion complexity affects drug-eluting stent (DES) outcomes according to diabetic status.

Background Previous studies have reported conflicting results regarding DES safety and efficacy in patients with and without diabetes mellitus (DM).

Methods Patient-level data from 18 prospective randomized trials were pooled. DES treatment outcomes in patients with versus without DM were analyzed in 2 propensity score–matched groups further stratified according to lesion complexity (American College of Cardiology and American Heart Association class A/B1 vs. B2/C). Remaining baseline differences were adjusted for by multivariate analysis.

Results DM was present in 3,467 of 18,441 patients (18.8%). DM was a predictor of 1-year repeat revascularization (target lesion revascularization: hazard ratio: 1.34; 95% confidence interval: 1.05 to 1.70; target vessel revascularization: hazard ratio: 1.40; 95% confidence interval: 1.15 to 1.72) and cardiac death or myocardial infarction (hazard ratio: 1.40; 95% confidence interval: 1.09 to 1.81). Rates of target lesion and target vessel revascularization were significantly higher in patients with versus those without DM with type B2/C lesions (8.0% vs. 4.5% and 10.6% vs. 5.9%, respectively, $p < 0.0001$ for both), but not in patients with only type A/B1 lesions (4.6% vs. 4.8%, $p = 0.87$, and 7.4% vs. 6.8%, $p = 0.47$, respectively), with a significant interaction between DM and lesion type observed for both endpoints ($p = 0.01$ and $p = 0.02$, respectively). No interaction was observed for death or myocardial infarction ($p = 0.28$).

Conclusions In the DES era, patients with DM remain at increased risk for cardiac death or myocardial infarction. However, DM is a risk factor for repeat revascularization only in those patients with complex lesions; patients with DM and noncomplex lesions have similar rates of 1-year freedom from repeat revascularization as do patients without DM. (J Am Coll Cardiol 2014;63:2111–8) © 2014 by the American College of Cardiology Foundation

Diabetes mellitus (DM) is a well-established predictor of angiographic restenosis and ischemia-driven target lesion revascularization (TLR) and target vessel revascularization (TVR) after percutaneous coronary intervention (PCI) with bare-metal stents (BMS) (1,2). Drug-eluting stents (DES) significantly reduce restenosis rates in patients with and those without DM, compared with BMS (3–6). Some

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Abbreviations and Acronyms

ACC = American College of Cardiology
AHA = American Heart Association
BMS = bare-metal stent(s)
CABG = coronary artery bypass grafting
CI = confidence interval
DES = drug-eluting stent(s)
DM = diabetes mellitus
HR = hazard ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
TLR = target lesion revascularization
TVR = target vessel revascularization

studies comparing outcomes after PCI with DES suggest than DM is no longer a correlate of restenosis (7,8), whereas others still identify DM as a predictor of TLR and TVR (9). Whether the efficacy of DES in eliminating diabetes as a risk factor for restenosis depends on lesion complexity is unknown. In this regard, lesions in patients with DM are known to be longer and present in smaller vessels than in patients without DM (10). It is thus conceivable that DM is a risk factor for restenosis given the propensity for more complex lesions in this condition and that DM might not predict adverse outcomes after controlling for lesion complexity. We therefore analyzed the efficacy and safety of DES from a large patient-level pooled database of 18,471 patients from 18 prospective randomized trials and examined the impact of DM on patient outcomes as a function of baseline lesion complexity.

Methods

To perform a comprehensive, patient-level pooled analysis, we combined 18 databases maintained at the Cardiovascular Research Foundation from prospective, randomized trials in which 1-year follow-up of patients treated with DES was available. The designs of these specific trials have been previously described and are summarized in Table 1 (3–5,11–25). One-year follow-up was completed in all trials, comprising the follow-up period for this study. The TAXUS, SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions), and ENDEAVOR series of trials evaluated the use of first-generation paclitaxel-eluting, sirolimus-eluting, and zotarolimus-eluting stents, respectively, compared with BMS or other DES, whereas the SPIRIT (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) series of trials and COMPARE (Comparison of the Everolimus Eluting XIENCE-V Stent With the Paclitaxel Eluting TAXUS LIBERTÉ Stent in All-Comers: A Randomized Open Label Trial) compared a second-generation everolimus-eluting stent with the first-generation paclitaxel-eluting stent. The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial compared 3 different pharmacological treatments in patients with moderate-risk and high-risk acute coronary syndromes who underwent invasive treatment. Stent choice (BMS or first-generation DES) was at the discretion of the operator. In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, patients presenting with ST-segment elevation were randomized to PCI with the first-generation paclitaxel-eluting stent versus an otherwise identical BMS stent.

Endpoints and statistical methods. Because the purpose of this study was to analyze DES outcomes in patients with versus without DM, only DES-treated patients were included in this analysis. Efficacy endpoints were rates of TLR and TVR. We also examined the rates of TVR-non-TLR (i.e., TVR remote from the target lesion). Safety endpoints were all-cause death, cardiac death, myocardial infarction (MI), definite and probable stent thrombosis (as defined by the Academic Research Consortium) (26), and composite cardiac death or MI. Major adverse cardiac events (MACE) were defined as the composite of all-cause death, MI, or TVR. TLR was defined as any repeat revascularization procedure (percutaneous or surgical) of the original target lesion site, including the stent and 5-mm proximal and distal margins. TVR was defined as any revascularization procedure occurring within the major epicardial vessel in which the stent was implanted or its branches. TVR-non-TLR was defined as any TVR occurring outside the TLR segment, as described earlier. Events as adjudicated in each trial were used for the pooled analysis. All analyses are by intention to treat.

Outcomes of all patients treated with DES were evaluated according to the presence of medically treated DM. To evaluate the impact of baseline lesion severity on efficacy and safety endpoints, patients with American College of Cardiology (ACC) and American Heart Association (AHA) classification A/B1 lesions versus those with any B2/C lesions were compared in the DM and non-DM cohorts (27). Patients with multiple PCI lesions were included in the B2/C group if at least 1 lesion was B2 or C in complexity; otherwise, they were included in the A/B1 group. To minimize differences in baseline characteristics of patients with and those without DM, 2 equal-sized propensity score–matched groups were created on the basis of the following variables: sex, hypertension, hyperlipidemia, previous MI, previous PCI, clinical syndrome at presentation, and stent type. The C-statistic for this model was 0.64. Stepwise Cox proportional-hazards multivariate analysis was performed to further correct for baseline differences that remained despite the propensity matching, adjusting for baseline Thrombolysis in Myocardial Infarction flow and baseline reference vessel diameter. Interactions between DM and ACC/AHA lesion type on 1-year major safety and efficacy outcomes were examined.

Categorical outcomes were compared using chi-square tests. Continuous variables are presented as mean ± SD and were compared using Student *t* tests. Cumulative event rates were estimated using time-to-event methods and were compared using the log-rank test. A p value <0.05 was considered statistically significant. All analyses were performed in SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Table 1 Description of the Prospective Randomized Pooled Trials

Trial (Ref. #)	Comparison	Randomization	Powered for	Primary Endpoint
ACUITY (11)	3 drug arms	1:1:1	Noninferiority and superiority	Death, MI, unplanned ischemic revascularization
COMPARE (12)	EES vs. PES	1:1	Superiority	Death, MI, TVR at 1 yr
C-SIRIUS (13)	SES vs. BMS	1:1	Superiority	In-stent MLD at 8 months
ENDEAVOR II (14)	PC-ZES vs. BMS	1:1	Superiority	TVF at 9 months
ENDEAVOR III (15)	PC-ZES vs. SES	1:3	Noninferiority	Late luminal loss at 8 months
ENDEAVOR IV (16)	PC-ZES vs. PES	1:1	Noninferiority	TVF at 9 months
E-SIRIUS (17)	SES vs. BMS	1:1	Superiority	In-stent MLD at 8 months
HORIZONS-AMI (18)	PES vs. BMS	3:1	Superiority and noninferiority	TLR at 12 months; death, MI, stroke, or ST
RAVEL (3)	SES vs. BMS	1:1	Superiority	In-stent late luminal loss at 6 months
SIRIUS (4)	SES vs. BMS	1:1	Superiority	TVF at 9 months
SPIRIT II (19)	EES vs. PES	3:1	Noninferiority	In-stent late loss at 6 months
SPIRIT III (20)	EES vs. PES	2:1	Noninferiority or superiority	In-segment late loss at 9 months
SPIRIT IV (21)	EES vs. PES	2:1	Noninferiority or superiority	TLF at 1 yr
TAXUS I (22)	PES vs. BMS	1:1	—	Death, MI, TVR, ST at 12 months
TAXUS II (23)	PES vs. BMS	1:1	Superiority	Neointimal proliferation by IVUS at 6 months
TAXUS IV (4)	PES vs. BMS	1:1	Superiority	Ischemia-driven TVR at 9 months
TAXUS V (24)	PES vs. BMS	1:1	Superiority	Ischemia-driven TVR at 9 months
TAXUS VI (25)	PES vs. BMS	1:1	Superiority	Ischemia-driven TVR at 9 months

All trials except COMPARE were multicenter.

ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; BMS = bare-metal stents; COMPARE = Comparison of the Everolimus Eluting XIENCE-V Stent With the Paclitaxel Eluting TAXUS LIBERTÉ Stent in All-Comers: A Randomized Open Label Trial; C-SIRIUS = Canadian Study of the Sirolimus-Eluting Stent in the Treatment of Patients With Long De Novo Lesions in Small Native Coronary Arteries; DES = drug-eluting stent; EES = everolimus-eluting stent; ENDEAVOR = Randomized Comparison of Zotarolimus-Eluting and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease; HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; IVUS = intravascular ultrasound; MI = myocardial infarction; MLD = minimal luminal diameter; PC-ZES = phosphorylcholine polymer-based zotarolimus-eluting stent; PES = paclitaxel-eluting stents; RAVEL = Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions; SES = sirolimus-eluting stents; SIRIUS = Sirolimus-Eluting Stent in De Novo Native Coronary Lesions; SPIRIT = Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions; ST = stent thrombosis; TAXUS = Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent; TLF = target lesion failure (defined as cardiac death, target vessel MI, or ischemia-driven TLR); TLR = target lesion revascularization; TVF = target vessel failure (defined as cardiac death, target vessel MI, or TVR); TVR = target vessel revascularization.

Results

Baseline characteristics. Of 32,644 patients enrolled in the 18 randomized trials, 18,475 were treated with DES. Among these patients, DM status was known for 18,441 patients (99.8%), of whom 3,467 (18.8%) had medically treated DM. Matches were found for 3,167 patients with DM, and thus a total of 6,334 patients constituted the analysis population. The baseline clinical angiographic and procedural characteristics for these patients are shown in Tables 2 and 3. The majority of patients (64.1%) were men, and the mean age was 63 years. The proportion of lesions defined by the ACC/AHA classification was similar between the DM and non-DM groups, although diabetic vessels were slightly smaller. Lesion severity and length were well matched between the 2 groups, however, as were procedural outcomes.

Clinical outcomes. As shown in Table 4, there were no significant differences in any endpoint according to diabetic status at 30 days. At 1 year, TVR rates were significantly increased in patients with DM, because of higher rates of both TLR and TVR-non-TLR. Similarly, the 1-year rates of mortality (both cardiac and noncardiac) and stent thrombosis (both definite and probable) were significantly higher in patients with DM, with a trend toward more MI. On multivariate analysis, DM was an independent predictor of TLR (hazard ratio [HR]: 1.34; 95% confidence interval [CI]: 1.05 to 1.70; $p = 0.02$), TVR (HR: 1.40; 95% CI: 1.15 to 1.72; $p = 0.001$), cardiac death or MI (HR: 1.40; 95% CI: 1.09 to 1.81; $p = 0.01$), and MACE (HR: 1.40; 95% CI: 1.19 to 1.65; $p < 0.0001$). In a propensity-adjusted multivariate analysis, there were no differences in the 1-year rates of death, MI, TLR, TVR, stent thrombosis, and composite MACE between patients with DM treated with versus without insulin (data not shown).

Outcomes according to ACC/AHA lesion subtype. As shown in Figure 1, TLR and TVR rates were increased in type B2/C compared with A/B1 lesions in the DM cohort but not in the non-DM cohort. A significant interaction was found between DM and ACC/AHA lesion type for the 1-year rates of TLR ($p_{interaction} = 0.01$) and TVR ($p_{interaction} = 0.02$). Conversely, the rates of cardiac death or MI and MACE were consistently higher in patients with compared with those without DM, with no interactions present between DM and ACC/AHA lesion class for either endpoint ($p_{interaction} = 0.28$ for both). The overall safety and efficacy interactions between DM status and ACC/AHA lesion complexity were consistent when lesion types A, B1, B2, and C were analyzed separately (data not shown).

Discussion

The present study, the largest to date examining DES outcomes according to the presence of DM, demonstrates that DM remains an independent predictor of clinical restenosis (i.e., both TLR and TVR), as well as adverse

Table 2 Baseline Clinical, Angiographic, and Stent Characteristics

Variable	DM (n = 3,167)	No DM (n = 3,167)	p Value
Age (yrs)	63.1 ± 10.6	63.2 ± 10.8	0.83
Men	2,013 (63.6%)	2,047 (64.6%)	0.37
Insulin treatment	880 (27.8%)	0 (0.0%)	<0.0001
Smoking (current)	688/2,872 (24.0%)	848/2,879 (29.5%)	<0.0001
Hypertension	2,620 (82.7%)	2,626 (82.9%)	0.84
Hyperlipidemia	2,479 (78.3%)	2,492 (78.7%)	0.69
Prior MI	786 (24.8%)	780 (24.6%)	0.86
Prior PCI	851 (26.9%)	856 (27.0%)	0.89
Prior CABG	382/3,166 (12.1%)	284/3,166 (9.0%)	<0.0001
ACC/AHA lesion type, worst			
Type A	182/3,084 (5.9%)	196/3,083 (6.4%)	0.46
Type B1	830/3,084 (26.9%)	799/3,083 (25.9%)	0.37
Type B2	936/3,084 (30.4%)	949/3,083 (30.8%)	0.71
Type C	1,136/3,084 (36.8%)	1,139/3,083 (36.9%)	0.93
Pre procedural TIMI flow grade, worst vessel			
0/1	346/3,091 (11.2%)	372/3,092 (12.0%)	0.30
2	236/3,091 (7.6%)	278/3,092 (9.0%)	0.05
3	2,620/3,091 (84.8%)	2,558/3,092 (82.7%)	0.03
Treated lesions	1.32 ± 0.59	1.28 ± 0.60	0.02
Treated vessels	1.16 ± 0.39	1.15 ± 0.38	0.31
Total number of stents	1.44 ± 0.80	1.42 ± 0.79	0.53

Values are mean ± SD or n (%).
ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass grafting; DM = diabetes mellitus; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

safety events, including cardiac death or MI, in the DES era. However, a strong interaction was present such that rates of TLR and TVR were increased in patients with versus those without DM with complex lesions (ACC/AHA class B2/C), but not in patients with more simple lesions (A/B1). No interaction was present between lesion complexity and the presence of diabetes on safety outcomes, although patients with DM had higher rates of

Table 3 Lesion Characteristics Before and After Intervention

Variable	DM (n = 3,731)	No DM (n = 3,653)	p Value
Pre-procedural			
Reference vessel diameter (mm)	2.70 ± 0.50	2.74 ± 0.49	0.002
MLD (mm)	0.74 ± 0.43	0.75 ± 0.45	0.40
Diameter stenosis (%)	72.4 ± 14.5	72.4 ± 15.1	0.98
Lesion length (mm)	15.4 ± 8.1	15.3 ± 8.1	0.59
TIMI flow grade			
0/1	374/3,724 (10.0%)	399/3,621 (11.0%)	0.17
2	270/3,724 (7.3%)	296/3,621 (8.2%)	0.14
3	3,080/3,724 (82.7%)	2,926/3,621 (80.8%)	0.03
Moderate or severe calcification	1,056/3,702 (28.5%)	985/3,600 (27.4%)	0.27
Moderate or severe tortuosity	118/1,926 (6.1%)	155/2,019 (7.7%)	0.06
Baseline total occlusions	278/2,209 (12.6%)	299/2,307 (13.0%)	0.71
Post-procedural (final)			
TIMI flow grade			
0/1	13/2,895 (0.4%)	17/2,741 (0.6%)	0.38
2	80/2,895 (2.8%)	78/2,741 (2.8%)	0.85
3	2,802/2,895 (96.8%)	2,646/2,741 (96.5%)	0.60
Reference vessel diameter (mm)	2.75 ± 0.50	2.82 ± 0.51	<0.0001
MLD (mm)	0.74 ± 0.43	0.75 ± 0.45	0.40
Diameter stenosis (%)	72.36 ± 14.48	72.37 ± 15.12	0.98

Values are mean ± SD, n/total n affected (%), or n (%).
Abbreviations as in Tables 1 and 2.

Table 4 Clinical Outcomes at 30 Days and 1 Year According to Diabetic Status

Outcome	DM (n = 3,167)	No DM (n = 3,167)	HR (95% CI)	p Value
30-day outcomes				
Death	0.7% (22)	0.4% (12)	1.84 (0.91–3.71)	0.08
Cardiac	0.6% (20)	0.3% (10)	2.01 (0.94–4.29)	0.07
Noncardiac	0.1% (2)	0.0% (1)	2.01 (0.18–22.14)	0.56
MI	2.8% (82)	2.4% (75)	1.09 (0.80–1.49)	0.58
ST				
Definite	0.5% (17)	0.4% (12)	1.42 (0.68–2.98)	0.35
Probable	0.3% (9)	0.1% (3)	3.01 (0.82–11.13)	0.08
Definite or probable	0.8% (26)	0.5% (15)	1.74 (0.92–3.28)	0.08
TVR	1.2% (38)	1.2% (30)	1.27 (0.79–2.05)	0.33
TLR	1.0% (31)	1.0% (23)	1.35 (0.79–2.31)	0.28
TVR-non-TLR	0.2% (7)	0.2% (7)	1.00 (0.35–2.86)	1.00
Cardiac death or MI	3.4% (101)	2.6% (82)	1.23 (0.92–1.65)	0.16
MACE	4.0% (119)	3.4% (99)	1.20 (0.92–1.57)	0.18
1-yr outcomes				
Death	2.6% (79)	1.4% (42)	1.91 (1.32–2.78)	0.0005
Cardiac	1.5% (47)	0.8% (25)	1.91 (1.17–3.10)	0.008
Noncardiac	1.0% (29)	0.5% (16)	1.85 (1.01–3.41)	0.04
MI	4.1% (126)	3.2% (100)	1.27 (0.98–1.65)	0.07
Any ST				
Definite	1.0% (30)	0.5% (17)	1.79 (0.99–3.24)	0.05
Probable	0.4% (12)	0.1% (4)	3.03 (0.98–9.39)	0.04
Definite or probable	1.4% (42)	0.7% (21)	2.02 (1.20.3.42)	0.007
TVR	9.4% (284)	6.2% (191)	1.54 (1.28–1.85)	<0.0001
TLR	6.8% (205)	4.6% (141)	1.50 (1.21–1.86)	0.0002
TVR-non-TLR	2.6% (79)	1.6% (50)	1.62 (1.14–2.31)	0.007
Cardiac death or MI	5.3% (164)	3.8% (120)	1.38 (1.09–1.75)	0.007
MACE	13.9% (429)	9.4% (294)	1.50 (1.29–1.74)	<0.0001

Events are % (n) determined using the Kaplan-Meier method.
CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular events (death, MI, or TVR). Other abbreviations as in Tables 1 and 2.

cardiac death, MI, and stent thrombosis than those without DM.

Our analysis, with 6,334 propensity-matched patients, was adequately powered to study the impact of DM after DES treatment for both safety and efficacy endpoints. Although it is well accepted that DM is a risk factor for adverse outcomes after PCI, in the present analysis, the presence of complex lesions, in both patients with and without DM, was also shown to predict death or MI. Moreover, the relative rates of TLR and TVR after DES according to DM status have been uncertain, with prior studies reporting conflicting results (7–9). The present large-scale study, representing a patient population with a broad spectrum of clinical presentations varying from stable angina pectoris to ST-segment elevation MI, demonstrates that DM is a strong predictor of TLR and TVR with DES. However, this finding was confined to patients with complex lesions (ACC/AHA type B2/C), in whom DM was associated with an approximate 80% increase in TLR and TVR at 1 year compared with those without DM. By contrast, the 1-year rates of TLR and TVR in patients with and without DM and more simple lesions (ACC/AHA type A/B1) were excellent (about 95% freedom from revascularization at 1 year) and nearly identical. This interaction between diabetes and lesion complexity on efficacy outcomes after DES might also in part explain the disparate findings in the previous studies (7–9).

A notable finding of the present study was the significantly higher 1-year TVR-non-TLR rates observed in patients with versus those without DM. This finding suggests that lesion progression may occur more rapidly in patients with DM, although the absence of routine follow-up angiography in the present study precludes knowing this definitively. Alternatively, it is also possible that patients with DM had more diffuse disease at baseline (with less complete initial revascularization), requiring additional PCI procedures within the first year. More rapid lesion progression and/or lower rates of complete revascularization at the time of the index procedure may in part contribute to the superior outcomes of coronary artery bypass grafting (CABG) compared with PCI in patients with DM, as recently reported from the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (28). In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study,

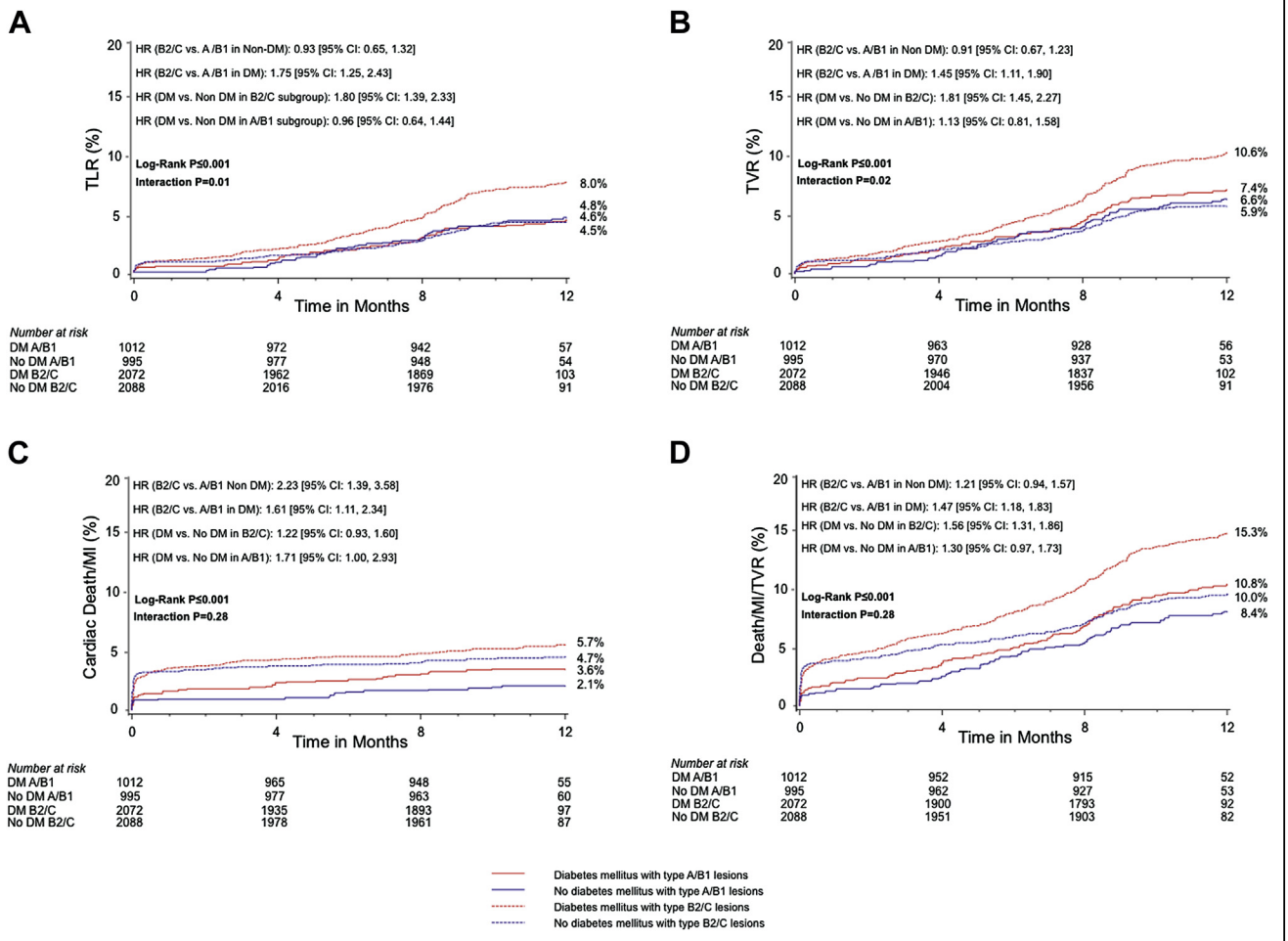

Figure 1 **Time-to-Event Curves According to the Presence or Absence of DM and Type A/B1 or Type B2/C Lesion**

(A) Target lesion revascularization (TLR); **(B)** target vessel revascularization (TVR); **(C)** cardiac death or myocardial infarction (MI); and **(D)** death, MI, or TVR. CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio.

DM (particularly insulin-treated DM) was a strong predictor of unanticipated adverse events originating from untreated angiographically mild nonculprit lesions (29). Conversely, incomplete revascularization is frequent after PCI and has been strongly linked to subsequent death, MI, and TVR (30,31). It remains speculative whether more complete revascularization (perhaps guided with fractional flow reserve to target ischemic lesions) (32) could thus improve outcomes in patients with DM.

In contrast to the findings regarding repeat revascularization, no significant relationship was present between the presence of diabetes, lesion type, and cardiac death or MI. Of note, the rate of cardiac death or MI was higher in both patients with DM and those without DM with type B2/C lesions. Thus, enhanced secondary prevention therapies are necessary to further reduce rates of death and MI after DES implantation in both patients with and without DM.

Differences in atherosclerotic plaque composition in patients with versus those without DM have been reported. Marso et al. (33) reported from PROSPECT that the extent of untreated atherosclerosis, calcification, and the amount of necrotic core (as assessed by radiofrequency intravascular ultrasound) were greater in patients with either DM or metabolic syndrome than in those without DM, findings that were associated with a higher 3-year rate of MACE. Similarly, Zheng et al. (34) showed that the atherosclerotic plaques in patients with DM or metabolic syndrome compared with patients without DM had larger necrotic cores and plaque burden and a higher percentage of thin-cap fibroatheromas, features that have been strongly related to plaque rupture (35). These reports have been recently verified using optical coherence tomography (36). Whether such angiographically mild lesions benefit by treatment with either PCI or CABG, however, is unknown.

The findings of the present study demonstrate favorable intermediate-term results in patients with DM after treatment of noncomplex lesions with DES. Unfortunately, patients with DM often present with advanced coronary artery disease and left ventricular dysfunction, due in part to impaired sensory perception of ischemia. Because the global incidence of DM is increasing, randomized trials focusing on the early detection and treatment of atherosclerotic coronary disease in patients with DM might be warranted to determine whether earlier revascularization with DES or CABG, coupled with improved systemic therapies, might improve prognosis in DM.

Study limitations. Because they derive from a post-hoc patient-level pooled analysis from 18 randomized trials, the present results should be considered hypothesis generating. Although the majority of patients were enrolled in trials without angiographic follow-up, in some of the older trials, this was not the case, and an effect of the "oculostenotic reflex" (which might be exaggerated in patients with DM) cannot completely be excluded. Moreover, minor interstudy variations in MI definition may have reduced the precision of this endpoint. The present study was not powered to examine the impact different types of first-generation and/or second-generation DES might have had on the interaction between DM status and lesion complexity (although stent type was used as a variable for the propensity score match to minimize the impact of any such effects). In this regard, although a network meta-analysis of randomized trials suggested that everolimus-eluting stents might be the safest and most efficacious in patients with DM (37), a recent nationwide study did not show substantial differences in clinical restenosis rates between different stent types in patients with DM (38). Propensity matching might have resulted in a non-DM cohort with a more severe risk-factor profile at baseline than the general non-DM population, which in turn might have muted the differences between groups. However, our intention was to study the impact of DM independent of other related risk factors. Baseline renal insufficiency was not uniformly reported, and therefore, this variable could not be incorporated into the propensity score matching. Perhaps most important, follow-up was truncated at 1 year, and thus whether these results apply to longer durations of follow-up after PCI is not known.

Conclusions

The present analysis, representing the largest study to date examining DES outcomes in patients with and without DM, demonstrates that DM remains an independent predictor of adverse safety and efficacy outcomes in the DES era. However, freedom from repeat revascularization 1 year after DES is comparable in patients with and those without DM with simple lesions treated with DES, whereas patients with DM with complex lesions have significantly higher rates of repeat revascularization after DES than those without DM. These data suggest that PCI might have favorable results compared with CABG if the extent of disease is not great, consistent with the results from the SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) trial (39). However, rates of cardiac death and MI are increased in patients with DM compared with those without DM, independent of lesion complexity, emphasizing the need for earlier detection and more effective systemic therapies in patients with this high-risk condition.

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